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PATENT & TRADEMARK OFFICE

TRANSMITTAL LETTER (General - Patent Pending)	Docket No. 2035.750

In Re Application Of: **Wisniewski et al.**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
10/057,610	01/25/2002	John K. Ford	23405	3743	3124

Title: **FREEZING AND THAWING OF BIOPHARMACEUTICALS WITHIN A VESSEL HAVING A REMOVEABLE STRUCTURE WITH A CENTRALLY POSITIONED PIPE**

COMMISSIONER FOR PATENTS:

Transmitted herewith is:

* **Transmittal Letter (General - Patent Pending) (1 Page)**
* **Response to Notification of Non-Compliant Appeal Brief and Appellant's Amended Appeal Brief (26 Pages)**
* **Copy of Declaration of Chris J. Burman (3 Pages)**
* **Copy of Declaration of V. Bryan Lawlis, Jr. (3 Pages)**
* **Copy of Declaration of David A. Vetterlein (3 Pages)**
* **Copy of Declaration of Richard Wisniewski (4 Pages) and Exhibits A-D**
* **Copy of Second Declaration of Richard Wisniewski (4 Pages)**

in the above identified application.

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Signature

Dated: **December 19, 2006**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Wisniewski et al.	**Group Art Unit:**	3743
Serial No.:	10/057,610	**Examiner:**	John K. Ford
Filed:	January 25, 2002	**Appeal No.:**	

Title: FREEZING AND THAWING OF BIOPHARMACEUTICALS WITHIN A VESSEL HAVING A REMOVEABLE STRUCTURE WITH A CENTRALLY POSITIONED PIPE

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on December 19, 2006.

Brett M. Hutton
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Date of Signature: December 19, 2006

To: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Response to Notification of Non-Compliant Appeal Brief and Appellant's Amended Appeal Brief
To the Board of Patent Appeals and Interferences

Dear Sir:

This communication is being filed in Response to the Notification of Non-Compliant Appeal Brief dated November 30, 2006, and supplements the Brief of

Appellant filed on June 14, 2004. The one month due date to file a response is November 23, 2006. Accordingly, this response is timely filed.

Real Party In Interest

This application is assigned to **Integrated Biosystems, Inc.** by virtue of an assignment executed on October 1, 1997 by the co-inventors and recorded with the United States Patent and Trademark Office on reel 9068, frame 0033. Therefore, the real party in interest is **Integrated Biosystems, Inc.**

Related Appeals and Interferences

To the knowledge of the appellant, appellant's undersigned legal representative, and the assignee, there are no interferences which will directly affect or be directly affected by or having a bearing on the Board's decision in the instant appeal. There are two other appeals that may be directly affected by or have a bearing on the Board's decision in the instant appeal. All of these appeals involve the same Examiner. These appeals involve the following applications.

Serial Number 08/895,936, notice of appeal filed April 19, 2004.
Serial Number 09/881,909, notice of appeal filed April 19, 2004.

The Board has not issued a decision in either of these appeals. Accordingly, there are no copies of any decisions rendered by a court or the Board in the proceedings identified above to be attached pursuant to 37 CFR 41.37(c)(1)(x).

Status of Claims

This patent application was filed on January 25, 2002 as a continuation application of U.S. Application Serial No. 08/895,936, which is still pending before the U.S. Patent Office before the same Examiner, and which is also being appealed. As filed, the application included nineteen (19) claims, of which two (2) were independent claims (i.e. claims 1 and 6).

In an initial Office Action dated September 9, 2002, claims 1-19 were subject to restriction and election requirement. The Examiner considered the apparatus claims (i.e. claims 6-19) and the method claims (i.e. claims 1-5) as two distinct inventions. In appellant's response dated October 9, 2002, appellant elected to pursue the method claims, claims 1-5 and newly added method claims 20-29, which include three (3) independent claims, namely claims 1, 20 and 25. In appellant's response dated October 9, 2002, no claims were amended.

In a second Office Action dated February 11, 2003, claims 1-5 and 20-29 were rejected under 35 U.S.C. §112, second paragraph, because the Examiner considered the term "biopharmaceutical product" ambiguous. These same claims were also rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of the 1992 publication by Wisniewski and Wu and the 1986 Kalhori and Ramadhyani article entitled "Studies on heat transfer from a vertical cylinder with or without fins, embedded in a solid phase change medium" and U.S. Patent No. 2,114,642 to West. In appellant's response dated April 14, 2003, claims 1, 20 and 25 were amended to recite that "at least a portion of the central axis of the elongated pipe is positioned coaxially with the central axis of the vessel."

Appellant received a final Office Action dated February 24, 2004 (almost five months after filing its response dated October 7, 2003) repeating the 35 U.S.C. §112, second paragraph, and 35 U.S.C. §103(a) rejections of claims 1-5 and 20-29.

A Notice of Appeal to the Board of Patent Appeals and Interferences was filed on April 19, 2004. The status of the claims is therefore as follows:

Claims allowed:	None
Claims objected to:	None
Claims rejected:	1-5 and 20-29
Claims canceled:	None

Claims withdrawn: 6-19

Appellant is appealing the rejection of claims 1-5 and 20-29.

Status of Amendments

Appellant proffered no response to the final Office Action dated February 24, 2004. The claims as set out in the Appendix include all prior entered amendments.

Summary of the Invention

In one aspect of the invention, as recited in claim 1, a method of preserving a biopharmaceutical product includes placing a medium comprising a biopharmaceutical product (e.g. [0110]) within a vessel (e.g. 4, FIG. 1; [0062]) having a central axis (e.g. FIG. 1) and an interior cavity (e.g. FIG. 1) defined by an interior wall (e.g. 10, FIG. 1; [0062]) of the vessel (e.g. 4, FIG. 1; [0062]); flowing a cooling fluid (e.g. [0064]) through a removably mounted heat exchange structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8) within the interior cavity (e.g. 10, FIG. 1; [0062]) of the vessel (e.g. 4, FIG. 1; [0062]), the structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8; FIG. 16a) comprising an elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) having a central axis (e.g. FIG 1; FIG. 8; FIG. 16; [0103]), wherein at least a portion of the central axis (e.g. FIG 1; FIG. 8; FIG. 16a) of the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) is positioned coaxially with the central axis (e.g. FIG. 1) of the vessel (e.g. 4, FIG. 1; [0062]) within the cavity (e.g. FIG. 1), the structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8) having one or more heat transfer members (e.g. 6, FIG. 1 and [0064]; 80, FIG. 8) thermally coupled thereto; and actively cooling (e.g. [0070]) the interior wall (e.g. 10, FIG. 1; [0062]) using a fluid (e.g. [0070]).

In a further aspect of the invention, the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) is tubular (e.g. FIGs. 1, 8 and 16a) and adapted to be actively cooled using a fluid (e.g. [0064]; [0089]; [0103]). In yet a further aspect of the invention, the one or more of the heat transfer members are fins (e.g. 6, FIG. 1; [0062]; FIG. 8 and [0089]). In yet a further aspect of the invention, the one or more of said fins (e.g. 6, FIG.

1; [0062]; FIG. 8 and [0089]) extend radially from said elongated pipe (e.g. FIG. 1 and FIG. 8)). In yet another aspect of the invention, the vessel (e.g. 4, FIG. 1; [0062]) comprises an open end which is closable by a removable top (e.g. FIG. 1), the structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8; FIG. 16a) being removable (e.g. [0015])through said open end (e.g. FIG. 1) of said vessel (e.g. 4, FIG. 1; [0062]).

In a further embodiment of the invention, as recited in claim 20, Appellant claims a method for facilitating the processing of a biopharmaceutical product comprising providing a vessel (e.g. 4, FIG. 1; [0062]) adapted to receive a medium comprising a biopharmaceutical product (e.g. [0110]) therein, the vessel (e.g. 4, FIG. 1; [0062]) having an interior cavity (e.g. FIG. 1) defined by at least an interior wall (e.g. 10, FIG. 1; [0062]) of the vessel (e.g. 4, FIG. 1; [0062]), the vessel (e.g. 4, FIG. 1; [0062]) having a central axis (e.g. FIG. 1). The method further comprises providing a passage (e.g. 22, FIG. 1; [0070]) for actively cooling the interior wall (e.g. 10, FIG. 1; [0062]) using a cooling fluid (e.g. [0070]). The method further comprises providing a heat exchange structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8) within the cavity (e.g. FIG. 1), the heat exchange structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8) including an elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) having a central axis (e.g. FIGs. 1, 8 and 16a), wherein at least a portion of the central axis (e.g. FIGs. 1, 8 and 16a) of the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) is positioned coaxially with the central axis (e.g. FIGs. 1, 8 and 16a) of the vessel (e.g. 4, FIG. 1; [0062]) within the cavity (e.g. FIG. 1), the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8) having one or more heat transfer members (e.g. 6, FIG. 1 and [0064]; 80, FIG. 8) thermally coupled thereto, the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) defining a passage (e.g. 12, FIG. 1; [0064]; FIG. 8; FIG. 16a) for actively cooling the one or more heat exchange members (e.g. 6, FIG. 1 and [0064]; 80, FIG. 8) using a cooling fluid (e.g. [0070]). In a further aspect of the invention, the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) is tubular (e.g. FIGs. 1, 8 and 16a) and adapted to be actively cooled using a fluid (e.g. [0064]; [0089]; [0103]). In yet a further aspect of the invention, the one or more of the heat transfer members are fins (e.g. 6, FIG. 1; [0062]; FIG. 8 and [0089]). In yet a further aspect of the invention, the one or more of said fins (e.g. 6, FIG.

1; [0062]; FIG. 8 and [0089]) extend radially from said elongated pipe (e.g. FIG. 1 and FIG. 8)). In yet another aspect of the invention, the vessel (e.g. 4, FIG. 1; [0062]) comprises an open end which is closable by a removable top (e.g. FIG. 1), the structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8; FIG. 16a) being removable (e.g. [0015]) through said open end (e.g. FIG. 1) of said vessel (e.g. 4, FIG. 1; [0062]).

In a further embodiment of the invention, as recited in claim 20, Appellant claims a method of processing a biopharmaceutical product comprising providing a vessel (e.g. 4, FIG. 1; [0062]) adapted to receive a medium comprising a biopharmaceutical product (e.g. [0110]) therein, the vessel (e.g. 4, FIG. 1; [0062]) having an interior cavity (e.g. FIG. 1) defined by an interior wall (e.g. 10, FIG. 1; [0062]) of the vessel (e.g. 4, FIG. 1; [0062]) and a heat exchange structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8) within the cavity (e.g. FIG. 1), the heat exchange structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8) having an elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) having a central axis (e.g. FIG. 1), wherein at least a portion of the central axis (e.g. FIG. 1) of the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) is positioned coaxially with the central axis (e.g. FIG. 1) of the vessel (e.g. 4, FIG. 1; [0062]) within the cavity (e.g. FIG. 1), the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8) having one or more heat transfer members (e.g. 6, FIG. 1; [0062]; FIG. 8 and [0089]) thermally coupled thereto; placing a medium comprising a biopharmaceutical product (e.g. [0110]) within the vessel (e.g. 4, FIG. 1; [0062]); actively cooling the interior wall (e.g. 10, FIG. 1; [0062]) using a cooling fluid (e.g. [0070]); actively cooling the heat exchange structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8) by flowing a fluid (e.g. [0064]) through the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]); and freezing the medium within the vessel (e.g. 4, FIG. 1; [0062]) to preserve said biopharmaceutical product (e.g. [0110]). In a further aspect of the invention, the elongated pipe (e.g. 12, FIG. 1; 81, FIG. 8; 602, FIG. 16a; [0103]) is tubular (e.g. FIGs. 1, 8 and 16a). In yet a further aspect of the invention, the one or more of the heat transfer members are fins (e.g. 6, FIG. 1; [0062]; FIG. 8 and [0089]). In yet a further aspect of the invention, the one or more of said fins (e.g. 6, FIG. 1; [0062]; FIG. 8 and [0089]) extend radially from said elongated pipe (e.g. FIG. 1 and FIG. 8)). In yet another aspect of the invention, the vessel (e.g. 4, FIG. 1; [0062])

comprises an open end which is closable by a removable top (e.g. FIG. 1), the structure (e.g. 8, FIG. 1 and [0064]; 81, FIG. 8; FIG. 16a) being removable (e.g. [0015]) through said open end (e.g. FIG. 1) of said vessel (e.g. 4, FIG. 1; [0062]).

Issues

1. Whether the term "biopharmaceutical product" is ambiguous under 35 U.S.C. §112, second paragraph.

2. Whether claims 1-5 and 20-29 were rendered obvious under 35 U.S.C. §103(a) by the combined teachings of the 1992 publication by Wisniewski and Wu ("the 1992 Wisniewski and Wu publication") and the 1986 Kalhori and Ramadhyani article entitled "Studies on heat transfer from a vertical cylinder with or without fins, embedded in a solid phase change medium" ("1986 Kalhori and Ramadhyani article") and U.S. Patent No. 2,114,642 to West ("the '642 patent").

3. Whether appellant satisfied its duty under Rule 56.

Grouping of Claims

Appellant respectfully submits that the claims 1-5 and 20-29 stand or fall together.

Argument

1. The Term "Biopharmaceutical Product" Is Not Ambiguous

As noted, claims 1-5 and 20-29 stand rejected under 35 U.S.C. §112, second paragraph, because the Examiner considered the term "biopharmaceutical product" ambiguous. Reversal of this rejection is respectfully requested.

Appellant did not provide a definition in the specification for the term "biopharmaceutical product." This term has a recognized meaning to those of ordinary skill in the art. The specification provided a number of examples of the type of biopharmaceutical products that may be processed by the present invention. The term "biopharmaceutical product" as set forth in the Specification in paragraph 29 includes, but is not limited to, proteins, cells, antibodies, medicines, plasma, blood, buffer solutions, viruses, serum, cell fragments, cellular components, and any other biopharmaceutical product.

Appellant also provided a definition of a "biopharmaceutical product" in a previous Amendment dated April 13, 2000 submitted in the parent Application Serial No. 08/895,936 as "a product derived from biological sources that has an intended therapeutic application and whose manufacturing is or will be regulated by pharmaceutical or veterinary regulatory agencies." This definition is supported by the Declarations of Chris J. Burman, V. Bryan Lawlis, Jr., and David A. Vetterlein ("the Declarants"), who are persons of ordinary skill in the art, which the Examiner is fully aware.

Despite support of the aforementioned understanding of the term of "biopharmaceutical products" from three persons of ordinary skill in the art having over 72 years of experience in the biotechnology and biopharmaceutical industry, the Office erroneously complicated the well recognized understanding of this term. For example, the Office sets forth an opinion in concluding that orange juice and milk are biopharmaceutical products. In particular, the Examiner makes an unsupported statement in the final Office Action on page 14 that "[b]lood *would probably* freeze more in the manner of orange juice or milk given its nearly macroscopic cellular nature whereas virus in a suitable buffer solution or water would freeze in the manner of pure or salty water." (emphasis added). Based on such reasoning and unsupported statements, the Office indicates that the definition offered by the Declarants appears to be unworkable. (See page 14 of the Office Action). However, when not defined by an applicant in the

specification, the words of a claim must be read as they would be interpreted by those of ordinary skill in the art, MPEP 2111.01, not by the Examiner himself.

In the final Office action, the Examiner also suggests that nothing in the declarations address why one designing freezing equipment for biopharmaceutical products disclosed in the specification would not look to the art of freezing water, orange juice or solids suspended in liquids. To the contrary, this issue has been addressed numerous times in previous responses and in the specification. As provided in the specification, appellant recognized, among other things, that the apparatus and method according to the aspects of the present invention are suited for use in processing biopharmaceutical products, as that term is understood by those of ordinary skill in the art. For example, the recited apparatus and method promotes uniform freezing at a rapid pace, which allows the biopharmaceutical product in the container to be frozen in as close to its native state as possible. (Specification, paragraph 32). Additionally, the present invention allows the freezing process to be done in a repeatable fashion so that a user can be assured that the freezing process is not causing batch to batch variations in the product. (Specification, paragraph 32).

Appellant respectfully submits that improper processing of biopharmaceutical product by, such as, for example, freezing and thawing, destroys biopharmaceutical products. In contrast, other products, such as, for example, orange juice, milk, water, particulate materials, and comestibles do not have the same processing concerns as biopharmaceutical products. Therefore, such products as orange juice, milk, water, particulate materials and comestibles, which do not require uniform freezing at a rapid pace which allow them to be frozen in as close to its native state as possible in order to prevent damage, are not included in the definition of biopharmaceutical products. In particular, the method or apparatus used to process (e.g. freeze or thaw) these other products is not critical and will not destroy these other products.

Appellant, however, recognizes that, for example, a "buffer solution" can indeed be a biopharmaceutical product depending upon the contents of such a solution. In lab chemistry, buffers are associated with the maintaining of certain pH levels, while biopharma vocabulary (which is relevant to this application) uses the term buffers very broadly, including buffers with proteins (like Human Serum Albumin) or amino acids (multiple amino acids are used, for example, lysine or arginine) clearly having biomolecules which can be damaged by improper freezing. It is readily apparent that buffer solutions which are biologically based may indeed be regulated and be a biopharmaceutical product. Appellant respectfully submits that if, for example, a particular buffer solution is not derived from biological sources nor regulated by FDA, then it would not be considered a biopharmaceutical product under the aforementioned understanding of the term. The list of potential biopharmaceutical products provided in the specification sets forth examples of products which may be biopharmaceuticals. Because the term has a recognized meaning within the art, it is readily apparent to one of ordinary skill in the art what the term "biopharmaceutical product" means.

Therefore, Appellant respectfully traversed the opinions set forth by the Office in the Office Actions that orange juice, milk, water, comestibles, particulate materials and any other non-biopharmaceutical products (e.g. orange juice and milk) relied upon by the Office Action are considered a biopharmaceutical product and that vessels that freeze such materials are relevant to the delicate preservation of biopharmaceutical products. Appellants also requested the Office to support, by a reference or affidavit pursuant to M.P.E.P. § 2144.04, its position and opinion or in contradiction to the above definition and Declarations by three Declarants of ordinary skill in the art. (See Applicants' Response dated April 13, 2003, page 9). Specifically, appellant requested that the Office show that products such as orange juice, milk and comestibles require uniform freezing at a rapid pace which allow them to be frozen in as close to its native state as possible in order to prevent damage. The Office ignored this request. Instead, the Examiner maintains his rejection and continues to rely on his own personal opinion and knowledge,

without providing a supporting reference or affidavit. (See pages 11-13 of the final Office Action).

Appellant respectfully submits that one of ordinary skill in the art is capable of distinguishing and classifying which products are and are not biopharmaceutical products based on the above definition, as evidenced by, for example, the Declarants classification of milk and orange juice as not being pharmaceutical products in their Declarations. For example, one of ordinary skill in the art is capable of determining which proteins, cells, antibodies, medicines, plasma, blood, buffer solutions, viruses, serum, cell fragments, cellular components, and any other biopharmaceutical product are considered a biopharmaceutical product under the above definition.

Finally, the reliance by the Office in the final Office Action (page 13) on an interpretation of a "would-be infringer" in rejecting the term "biopharmaceutical products" is improper. Under M.P.E.P. § 2173.02, definiteness of claim language must be analyzed in light of the content of the particular application disclosure, the teachings of the prior art and the claim interpretation that would be given *by one possessing the ordinary level of skill in the pertinent art at the time the invention was made*. Appellant respectfully submits that the proper inquire is how "biopharmaceutical product" will be interpreted by a person of ordinary skill in the art, not by a "would be" infringer. Therefore, the Office, in maintaining the rejection of the term "biopharmaceutical products" on this basis, failed to follow this approach.

Accordingly, Appellant respectfully submits that the term "biopharmaceutical product" is definite.

2. Claims 1-5 And 20-29 Are Patentable Over The Combined Teachings Of The 1992 Wisniewski And Wu Publication, The 1986 Kalhori And Ramadhyani Article And The '642 Patent

As noted, claims 1-5 and 20-29 stand rejected under 35 U.S.C. §103(a) as obvious over the combined teaching of the 1992 Wisniewski and Wu Publication, the 1986 Kalhori and Ramadhyani article and the '642 patent.

In support of this rejection, the Office relies on features in the cited prior art that are not recited in the claims. For example, the Office states that the heat exchange members in the 1992 Wisniewski and Wu publication are in "close spaced proximity" to the interior surface of the container. The Office also focuses on the lack of explicit disclosure in this publication of a "thermal bridge of ice", but vigorously argues that such a thermal bridge is inherently formed based on disclosures in other U.S. patents (See pages 16-20 of the final Office Action). Further, the Office points to both the 1992 Wisniewski and Wu article and the '642 patent to show compartmentation (e.g. fins configured to divide the tank into compartments). However, none of these features relied upon by the Office are recited in any of the independent or dependent claims of the present application. Specifically, none of the claims require the fins to be "in close spaced proximity" to the interior surface of the container or to divide the tank into compartments, or a "thermal bridge of ice". Instead, the appellants invention is directed to a heat exchange structure comprising an elongated pipe being centrally positioned (i.e. coaxially) within the cavity having one or more heat transfer members thermally coupled thereto.

a. The Office Improperly Combined The Cited References

Initially, appellant notes that each of the references relied upon by the Office to reject the claims teach completely different processes to freeze products by using completely different principles. In fact, the cited references teach away from each other and, therefore, there is no motivation or suggestion to combine. Further, aside from the 1992 Wisniewski and Wu publication, none of the cited references disclose biopharmaceutical products or recognize the problems associated with processing such products.

i. The 1992 Wisniewski and Wu Publication

Specifically, the 1992 Wisniewski and Wu publication discloses a device having an internal heat transfer coil pipe with fins welded to the external surface of the coil pipe. The fins attached to the coil are very small and thin and were designed only to aid the freezing around the loop coil in order to increase the relatively small surface area of the loop pipe (e.g. adding more cold surface area). The outside of this device is cooled. A copy of this device is reproduced, for convenience, below:

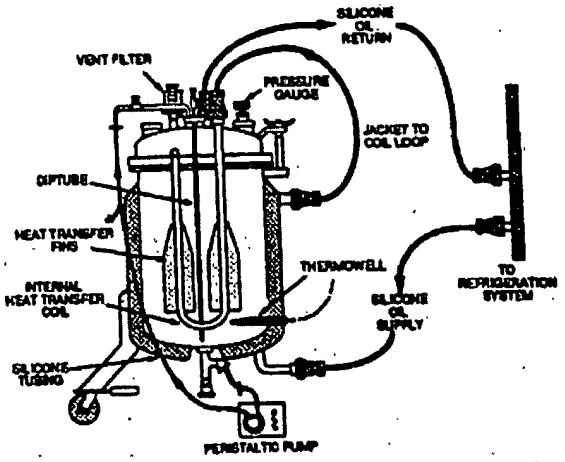


Figure 1. Freeze-thaw Vessel: Thawing Configuration

As shown, the fins attached to the pipe coil are very small and thin and were designed only to aid the freezing around the loop coil in order to increase the relatively small surface area of the loop pipe (e.g. adding more cold surface area). (Second Wisniewski Declaration, ¶8).

ii The 1986 Kalhori and Ramadyani Article

The 1986 Kalhori and Ramadyani article involves the investigation of the solidification of a paraffin[1] in a smooth, thin-walled metal cylindrical tank having an electrical strip heater wrapped around the upper part of the tank. The purpose of the

[1] Paraffin is a white, waxy, odorless, tasteless solid substance consisting of a mixture of straight chais saturated hydrocarbon used to make, for example, candles, sealing preserving jars, waterproofing paper

investigation was to demonstrate that natural convection in the liquid phase plays a dominant role in melting and to a certain extent influences freezing. The investigation involves a comparison of the temperature distributions in the paraffin using a plain vertical cylinder in the tank and a vertical cylinder with fins, during cyclic melting and freezing. This cyclic cooling and heating generates convectional currents in the liquid phase of the medium. There is no disclosure or suggestion that the external tank walls are actively cooled. In contrast, the vessel is wrapped with an electrical ban heater to warm the medium from the outside while the cylinder within is cooling it. Therefore, the temperature closer to the external wall from within the vessel increases, the temperature closer to the cylinder decreases, and heat transfer to the paraffin occurs from the cylinder.

The 1986 Kalhori and Ramadyani article simply concludes that the use of fins works better than no fins. However, this fact was already recognized in the 1992 Wisniewski and Wu publication as shown by the disclosure of the coil pipe having fins attached thereto. There is absolutely no disclosure or suggestion in the 1986 Kalhori and Ramadyani article of biopharmaceutical product or a discussion or recognition of the problems associated with processing biopharmaceutical product. Therefore, there is no motivation or suggestion to combine the 1986 Kalhori and Ramadyani article with the 1992 Wisniewski and Wu article because the 1986 Kalhori and Ramadyani article does not involve, or recognize the problems associate with processing, biopharmaceutical products.

There is also no motivation to combine the interior structure disclosed in the 1986 Kalhori and Ramadyani article with the container disclosed in the 1992 Wisniewski and Wu publication because the devices disclosed in both articles involve different principles of freezing. Specifically, the device disclosed in the 1992 Wisniewski and Wu article cools the container from the outside and the inside and the 1986 Kalhori and Ramadyani article heats the container on the outside while cooling the container inside. Therefore, contrary to the Examiner's suggestion, it would not be obvious to simply put the finned cylinder disclosed in the 1986 Kalhori and Ramadyani article in the tank disclosed in the

1992 Wisniewski and Wu publication because one of ordinary skill in the art would not be motivated to look towards the 1986 Kalhori and Ramadyani article to combine with the 1992 Wisniewski and Wu publication due to problems associated with processing biopharmaceutical products and the fact that the device in the 1992 Wisniewski and Wu article already uses fins and cools the device from the inside using the coil pipe.

In support of this combination, the Office simply concludes that it would be obvious to one of ordinary skill in the art to replace the heat exchanger and fins of the 1992 Wisniewski and Wu publication with the heat exchanger and fins shown in the 1986 Kalhori and Ramadhyani article to improve heat transfer and to facilitate ease of construction as well as to facilitate easy removal from the frozen mass. However, the Office fails to explain how substituting one structure for another in a vessel using completely different principles would produce the same desirable freezing results of biopharmaceutical products, especially in view of the Examiner's own statements on page 3 in the final Office Action dated February 24, 2004 that:

> It is respectfully submitted that these freezing phenomena are so complex that no human being including one with nearly 30 years of experience can accurately predict such results. Purporting to have such ability only diminishes ones credibility.

iii. The '642 Patent

The '642 patent is directed to the acceleration of the production of frozen articles such as milk, sherbet and similar substances, not to the preservation of biopharmaceutical products. The '642 patent describes freezing that prevents sugar deposition form the original solution. The object of this patent is not to optimize the preservation of biopharmaceutical products by freezing, but rather to fast freeze to make milk and sherbet look a certain way (e.g appealing to consumers). In the '642 patent, liquid refrigerant gets to the header (3) where it boils in cup (15) onto which the container with product (8) is slipped. Since the refrigerant boils inside the cups (15), then there is no control of

freezing (e.g. very fast freezing, see page 2, lines 60-66). Contrary to the Office's statements, the '642 patent does not show any cooling surface extensions such as fins or an elongated pipe.

iv. No Motivation To Combine

Therefore, the 1992 Wisniewski and Wu publication, the 1986 Kalhori and Ramadyani article and the '642 West patent each freeze products by completely different ways using completely different freezing principles. As such, these references teach away from each other and there is simply no motivation to combine the same. Specifically, the 1986 Kalhori and Ramadyani article teaches heating the medium from the outside of the cylinder while the structure within was cooling it. In sharp contrast, the 1992 Wisniewski and Wu publication teaches cooling the outside and inside of the cylinder. Finally, the '642 West patent discloses a method of freezing completely different from the device in the 1992 Wisniewski and Wu publication and the 1986 Kalhori and Ramadyani article. Appellant respectfully submits that one of ordinary skill in the art would not look towards a device that is heated on the outside to combine with a device that was cooled on the inside because the methods and principles of freezing used in both devices are completely different. This conclusion is reinforced by statements made by this same Examiner in the final Office Action of the parent application (Serial No. 08/895,936) highlighting the difficulty in determining the temperature distribution of these types of devices. These statements include the following:

> The Examiner . . . does not believe that there is anyone who can model or calculate these temperature profiles without the aid of sophisticated computers and/or experimental work. . . .The processes of modeling natural convection and moving-front phase change occurring together with sub-cooling is, to the Examiner's knowledge, is state of the art or beyond the state of the art in numerical solutions on computers. See Final Office Action in Serial No. 08/895,936, page 8.

> It is respectfully submitted that these freezing phenomena are so complex that no human being including one with nearly 30 years of experience can accurately

predict such results. Purporting to have such ability only diminishes ones credibility. See Final Office Action in Serial No. 08/895,936, page 10.

Thus, researchers, other than Mr. Wisniewski, state that accurate modeling of phase change heat transfer in tanks with finned element such as shown in Figure 3 of the K&R article can only be done by computers or by direct empirical measurement. See Final Office Action in Serial No. 08/895,936, page 11.

[T]he temperature distribution must either be measured or generated by very sophisticated computer programs, which have had their validity checked against measured data. See Final Office Action in Serial No. 08/895,936, page 12.

Mr. Wisniewski's guesswork even in declarative form is simply no substitute for real evidence. Neither he nor any other person on the planet is in a position to properly guess at the actual temperature distribution. See Final Office Action in Serial No. 08/895,936, page 14.

Accordingly, the Office admits that even those of ordinary skill in the art cannot look at and simply combine the cited references and arrive at the desired result disclosed in the Specification and recited in the claims of the present invention without experimentation or the aid of a computer. Therefore, there is simply no suggestion or motivation to combine the structure within the 1986 Kalhori and Ramadyani article with the cooled cylinder of the Genentech device.

The Office in its final Office Action ignored appellant's argument set forth in appellant's response dated April 14, 2003, and repeated above, concerning the different methods of freezing products disclosed in these cited references using completely different principles. Since the Office Action failed to address these arguments, appellant respectfully submits that this deficiency at least renders incomplete a rejection based on an alleged combination of the cited references. For at least this reason, reversal of the obviousness rejection and allowance of the claims are respectfully requested.

b. The Cited References Do Not Disclose The Recited Method

Appellant's independent claims recite: "said structure comprising an elongated pipe having a central axis, wherein at least a portion of the central axis of said elongated

pipe is positioned coaxially with the central axis of the vessel within said cavity." Appellant's independent claims also require active cooling of the interior wall of the vessel.

The 1992 Wisniewski and Wu publication fails to teach or suggest appellants' claimed element of an elongated pipe positioned coaxially with a central axis of the vessel. The Office concedes this in the final Office Action on page 15 by stating that this publication "lacks a 'spur tube' type cooler in the center. The 1986 Kalhori and Ramadyani article fails to disclose active cooling of the exterior wall of the vessel. In contrast, the device in this article heats the exterior wall. Finally, as explained above, the '642 patent describes a completely different apparatus and method for freezing non-biopharmaceutical products.

Therefore, in view of the reasons provided above, the 1992 Wisniewski and Wu publication, the 1986 Kalhori and Ramadyani article, and the '642 patent fails to disclose each and every limitation recited in the claims and there is no motivation or suggestion to combine these references.

3. Appellant Satisfied Their Duty Under Rule 56

In the second Office Action dated February 11, 2003, the Examiner requested additional information concerning the prior art devices disclosed in the specification and the Genentech device disclosed in the 1992 disclosure of Wisniewski and Wu. The Examiner also suggested that the inventors contact Genentech to obtain the dimensions of the prior art Genentech device. However, the Examiner incorrectly assumed that the appellants were in possession of this information because they worked on the Genentech device more than a decade ago.

In appellant's response dated April 14, 2003, appellant made clear to the Examiner that the applicants do not work for Genentech and were not in possession of the 1992 Genentech device. In an effort to further assist the Office, one of the inventors, Mr.

Wisniewski, submitted a Second Declaration that provided as much information that he could remember concerning the Genentech device.

In a third Office Action dated September 30, 2003, the Examiner considered appellant's response dated April 14, 2003 as not fully responsive to the second Office Action because the appellant failed to provide a copy of the first and second declarations of Mr. Wisniewski. The Examiner also suggested that applicants submit a third declaration to explain why they did not contact Genentech.

Appellant promptly filed a response on October 7, 2003 by submitting a copy of the first and second declarations and explaining that they have disclosed as much information as they can remember concerning the prior art, especially the Genentech device. Therefore, appellant has satisfied their duty under Rule 56 and the Office should have considered appellant's response to the third Office Action as a complete reply under 37 C.F.R. §1.105(a)(3).

In the final Office Action, the Examiner provides his personal response to each paragraph in the declarations submitted by Mr. Wisniewski. However, these declarations were not submitted to support the claims in the present application, but rather to contest the Examiner's accusations that appellant failed to provide information concerning the prior art, specifically the Genentech device disclosed in the 1992 Wisniewski and Wu article. A response to the Examiner's position concerning the substance of these declarations is not necessary at this point in time because, as mentioned above, the claims in the present application do not recite a "thermal bridge" or a relationship (in distance) between the fins and interior wall of the vessel.

Appellant provided the Office with as much information concerning the prior art that is presently know or readily available. Whether or not Genentech is a competitor or customer (both are actually true), Rule 56 does not require an applicant to contact another company for a competitive device in order to conduct experiments using its own

equipment to perform testing to support the Examiner's unsupported beliefs and speculation, which have no bearing upon the claims. Clearly, this request exceeds the requirement under Rule 56.

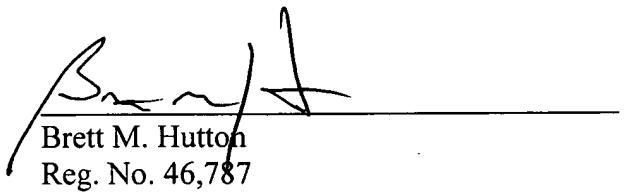
Therefore, appellant submits that all information that is known and readily available was submitted.

Conclusion

For the reasons set forth above, reversal of the rejections and allowance of this application are respectfully requested.

Dated: December 19, 2006

Respectfully submitted,



Brett M. Hutton
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APPENDIX

CLAIMS FOR APPLICATION SERIAL NUMBER 10/057,610

1. A method of preserving a biopharmaceutical product comprising:

placing a medium comprising a biopharmaceutical product within a vessel having an interior cavity defined by an interior wall of said vessel, said vessel having a central axis;

flowing a cooling fluid through a removably mounted heat exchange structure within said interior cavity of said vessel, said structure comprising an elongated pipe having a central axis, wherein at least a portion of the central axis of said elongated pipe is positioned coaxially with the central axis of the vessel within said cavity, said structure having one or more heat transfer members thermally coupled thereto; and

actively cooling said interior wall using a fluid.

2. The method of claim 1, wherein said elongated pipe is tubular and adapted to be actively cooled using a fluid.

3. The method of claim 1, wherein said one or more of said heat transfer members are fins.

4. The method of claim 3, wherein said one or more of said fins extend radially from said elongated pipe.

5. The method of claim 1, wherein said vessel comprises an open end which is closable by a removable top, said structure being removable through said open end of said vessel.

20. A method for facilitating the processing of a biopharmaceutical product comprising:

providing a vessel adapted to receive a medium comprising a biopharmaceutical product therein, said vessel having an interior cavity defined by at least an interior wall of said vessel, said vessel having a central axis;

providing a passage for actively cooling said interior wall using a cooling fluid; and

providing a heat exchange structure within said cavity, said heat exchange structure including an elongated pipe having a central axis, wherein at least a portion of the central axis of said elongated pipe is positioned coaxially with the central axis of the vessel within said cavity, said elongated pipe having one or more heat transfer members thermally coupled thereto, said elongated pipe defining a passage for actively cooling the one or more heat exchange members using a cooling fluid.

21. The method of claim 20, wherein said elongated pipe is tubular and adapted to be actively cooled using a fluid.

22. The method of claim 20, wherein said one or more of said heat transfer members are fins.

23. The method of claim 22, wherein said one or more of said fins extend radially from said elongated pipe.

24. The method of claim 20, wherein said vessel comprises an open end which is closable by a removeable top, said structure being removeable through said open end of said vessel.

25. A method of processing a biopharmaceutical product comprising:

providing a vessel adapted to receive a medium comprising a biopharmaceutical product therein, said vessel having an interior cavity defined by an interior wall of said vessel and a heat exchange structure within said cavity, said heat exchange structure having an elongated pipe having a central axis, wherein at least a portion of the central axis of said elongated pipe is positioned coaxially with the central axis of the vessel within said cavity, said elongated pipe having one or more heat transfer members thermally coupled thereto;

placing a medium comprising a biopharmaceutical product within said vessel;

actively cooling said interior wall using a cooling fluid;

actively cooling said heat exchange structure by flowing a fluid through the elongated pipe; and

freezing the medium within said vessel to preserve said biopharmaceutical product.

26. The method of claim 25, wherein said elongated pipe is tubular.

27. The method of claim 25, wherein said one or more of said heat transfer members are fins.

28. The method of claim 27, wherein said one or more of said fins extend radially from said elongated pipe.

29. The method of claim 25, wherein said vessel comprises an open end which is closable by a removeable top, said structure being removeable through said open end of said vessel.

Evidence Appendix

1) Declaration of Chris J. Burman – This declaration was entered and considered by the Examiner in the Office Action dated February 11, 2003.

2) Declaration of V. Bryan Lawlis, Jr. - This declaration was entered and considered by the Examiner in the Office Action dated February 11, 2003.

3) Declaration of David A. Vetterlein - This declaration was entered and considered by the Examiner in the Office Action dated February 11, 2003.

4) Declaration of Richard Wisniewski – This declaration was entered and considered by the Examiner in the Office Action dated February 11, 2003.

5) Second Declaration of Richard Wisniewski - This declaration was entered and considered by the Examiner in the Office Action dated February 11, 2003.

Related Proceedings Appendix

NONE

The Board has not issued a decision in either of the appeals identified above in the Section entitled "Related Appeals and Interferences."

Attorney Docket No. 17882-705

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	PATENT APPLICATION
Richard Wisniewski et al.	)	Group Art Unit: 3743
Application No.: 08/895,782	)	Examiner: Ford
Filed: July 17, 1997	)	
Title: FREEZING AND THAWING VESSEL WITH THERMAL BRIDGE FORMED BETWEEN CONTAINER AND HEAT EXCHANGER	)	**DATE**: October 8, 1999

DECLARATION UNDER 37 C.F.R. § 1.132

I, Chris J. Burman, declare as follows:

1. I received a B.Sc. in Applied Biology, Magna Cum Laude. I am currently Senior Vice President for Manufacturing & Process Sciences for IDEC Pharmaceuticals Corporation, where I am responsible for all aspects of process development and manufacturing for IDEC Pharmaceuticals, Inc.

2. Prior to my current position, I was Vice President for Manufacturing Sciences at IDEC Pharmaceuticals Corporation. Before that, I was Director of Manufacturing Technology for Life Sciences International, TPA Operations Manager for Genentech, Inc., and Manager and Senior Manager in the Production and Purification function at Wellcome Biotech, inc. In total, I have over 32 years of experience in various aspects of biotechnology, biopharmaceuticals, and general pharmaceutical development.

3. I am not a paid consultant, employee, or agent of the assignee of this patent application. I am not receiving compensation in exchange for providing this testimony.

5. I have read and understood U.S. Patent Nos. 5,609,035 to Cothern et al. ("Cothern"); 5,524,706 to Nakamura et al. ("Nakamura"); and 1,874,578 to Morrison ("Morrison").

6. I understand that, during the prosecution of the present invention, an issue has arisen regarding the definition of the term "biopharmaceutical product."

7. It is my opinion that an accurate and clear definition of biopharmaceutical product is: **a product derived from biological sources that has an intended therapeutic application and whose manufacturing is or will be regulated by pharmaceutical or veterinary regulatory agencies.**

8. It is my opinion that the Cothern, Nakamura, and Morrison references do not suggest nor teach biopharmaceuctical products, or devices or methods useful in processing biopharmaceutical products. In particular, it is my opinion that conventional milk, as disclosed in the Morrison reference, or conventional orange juice, as disclosed in the Cothern reference, are not biopharmaceutical products.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By: C J Burman
Chris J. Burman

Date: Oct. 6 1999
October 6, 1999

Country of Citizenship: ~~U.S.A.~~ UK
c/s

Residence: 19936, Sunset Oaks Drive
Ramona, CA 92065.

Post Office Address: Same as above

#17

Attorney Docket No. 17882-705

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	PATENT APPLICATION
Richard Wisniewski et al.	)	Group Art Unit: 3743
Application No.: 08/895,782	)	Examiner: Ford
Filed: July 17, 1997	)	
Title: FREEZING AND THAWING VESSEL WITH THERMAL BRIDGE FORMED BETWEEN CONTAINER AND HEAT EXCHANGER	)	**DATE**: October 8, 1999

DECLARATION UNDER 37 C.F.R. § 1.132

I, V. Bryan Lawlis, Jr., declare as follows:

1. I received a Ph.D. in Biochemistry from Washington State University in 1979. I am currently the Chairman of Covance Biotechnology Services, Inc.

2. Prior to my current position, I was President and Chief Executive Officer of Covance Biotechnology Services, Inc. I have 18 years experience in the biotechnology and biopharmaceutical industry where I have served in a variety of scientific and management positions brining a diverse array of biotechnology and biopharmaceutical products to market.

3. I am not a paid consultant, employee, or agent of the assignee of this patent application. I am not receiving compensation in exchange for providing this testimony.

5. I have read and understood U.S. Patent Nos. 5,609,035 to Cothern et al. ("Cothern"); 5,524,706 to Nakamura et al. ("Nakamura"); and 1,874,578 to Morrison ("Morrison").

6. I understand that, during the prosecution of the present invention, an issue has arisen regarding the definition of the term "biopharmaceutical product."

7. It is my opinion that an accurate and clear definition of biopharmaceutical product is: **a product derived from biological sources that has an intended therapeutic application and whose manufacturing is or will be regulated by pharmaceutical or veterinary regulatory agencies.**

8. It is my opinion that the Cothern, Nakamura, and Morrison references do not suggest nor teach biopharmaceuctical products, or devices or methods useful in processing biopharmaceutical products. In particular, it is my opinion that conventional milk, as disclosed in the Morrison reference, or conventional orange juice, as disclosed in the Cothern reference, are not biopharmaceutical products.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By: V. Bryan Lawlis, Jr.
V. Bryan Lawlis, Jr.

Date: October 7th, 1999
October 6, 1999

Country of Citizenship: U.S.A.

Residence: 400 Swan's Mill Crossing
Raleigh, NC 27614

Post Office Address: Same as above

Attorney Docket No. 17882-705

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	PATENT APPLICATION
Richard Wisniewski et al.	Group Art Unit: 3743
Application No.: 08/895,782	Examiner: Ford
Filed: July 17, 1997	
Title: FREEZING AND THAWING VESSEL WITH THERMAL BRIDGE FORMED BETWEEN CONTAINER AND HEAT EXCHANGER	**DATE**: October 8, 1999

DECLARATION UNDER 37 C.F.R. § 1.132

I, David A. Vetterlein, declare as follows:

1. I received a Ph.D. in Biochemistry from the University of California at Santa Barbara in 1977. I am currently the Director for Process Development and Manufacturing for ICOS Corporation, where I lead a department of 28 people that is responsible for clinical and market manufacturing of biological products and for process development.

2. Prior to my current position, I have been a Senior Scientist in the Recovery Process Research and Development group at Genentech, Inc., where I was involved in various aspects of product and process research for development of various biopharmaceuticals. In total, I have over 22 years of experience in various aspects of biotechnology, biopharmaceuticals, and general pharmaceutical development.

3. I am not a paid consultant, employee, or agent of the assignee of this patent application. I am not receiving compensation in exchange for providing this testimony.

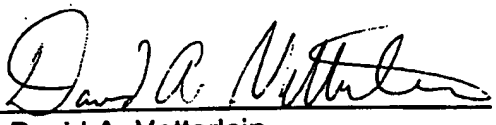
5. I have read and understood U.S. Patent Nos. 5,609,035 to Cothern et al. ("Cothern"); 5,524,706 to Nakamura et al. ("Nakamura"); and 1,874,578 to Morrison ("Morrison").

6. I understand that, during the prosecution of the present invention, an issue has arisen regarding the definition of the term "biopharmaceutical product."

7. It is my opinion that an accurate and clear definition of biopharmaceutical product is: **a product derived from biological sources that has an intended therapeutic application and whose manufacturing is or will be regulated by pharmaceutical or veterinary regulatory agencies.**

8. It is my opinion that the Cothern, Nakamura, and Morrison references do not suggest nor teach biopharmaceuctical products, or devices or methods useful in processing biopharmaceutical products. In particular, it is my opinion that conventional milk, as disclosed in the Morrison reference, or conventional orange juice, as disclosed in the Cothern reference, are not biopharmaceutical products.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By: 
David A. Vetterlein

Date: Oct. 6, 1999
October 6, 1999

Country of Citizenship: U.S.A.

Residence: 9620 146th Place SE, Snohomish, WA 98296

Post Office Address: Same as above

PATENT

ATTORNEY DOCKET NO.: 2035.706

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : WISNIEWSKI et al. Group Art Unit: 3743

Serial No.: 08/895,936 Examiner : John Ford

Filed : July 17, 1997

For : FREEZING AND THAWING VESSEL WITH THERMAL BRIDGE FORMED BETWEEN HEAT EXCHANGE MEMBERS

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF RICHARD WISNIEWSKI

1. I am one of the inventors of the above-referenced United States patent application. I am also a named inventor of six U.S. Patents relating to cryopreservation of biopharmaceuticals and numerous pending patent applications. I make the statements herein to the best of my own personal knowledge.

2. I received degrees in Mechanical Engineering and Chemical Engineering from Warsaw Technical University in Warsaw, Poland in 1971. I have over 26 years of experience in applied research, process and product development, process control, equipment and device design, industrial facility design and project and team management in the biopharmaceutical field.

3. I am a co-founder and currently the Chief Technology Officer of Integrated Biosystems, Inc.

4. Prior to my current position, I have held senior engineering and management positions with Wyeth-Ayerst, Genentech, Inc., Bepex Corporation and Ares Serono. While at

Genentech, Inc., I was a Principal Process Engineer responsible for pioneering work in the design of equipment and processes for biopharmaceutical manufacturing, including systems for cryopreservation, chromatography, filtration and bioreactors and aseptic processing used in large scale production.

5. I have published numerous articles in the areas of cryobiology and cryopreservation. While I was working for Genentech, Inc., I co-published, with Vincent L. Wu, an article entitled "Large-Scale Freezing and Thawing of Biopharmaceutical Drug Product" for the Advanced Technologies For Manufacturing Of Aseptic & Terminally Sterilized Pharmaceuticals & Biopharmaceuticals convention during the Proceedings of the International Congress in 1992 ("the 1992 article"). I have provided a copy of this article in Exhibit A. This 1992 article is similar to the 1996 article previously disclosed to the Patent Office during the prosecution of the above-reference application.

6. The 1992 article discloses a freeze-thaw vessel for biopharmaceutical products having an internal heat transfer coil with fins welded to the external surface of the coil pipe which I designed. The figure on page 134 of the article accurately depicts the heat transfer coil and fin arrangement within the vessel. This article does not disclose or suggest the formation of a thermal transfer bridge, as defined in the above-reference application, by the medium in a gap between the fins and the interior wall of the vessel, even after the medium in the gap is frozen.

7. In Exhibit B, I have provided a schematic representation of the freezing which would have occurred in the vessel disclosed in the 1992 article at a period in time before the medium between the fin and the interior wall of the vessel is frozen along with a graph showing the temperature distribution along the radius of the vessel. Exhibit B depicts a schematic sectional view of the interior of the vessel disclosed in the 1992 article. To the best of my knowledge the temperature graph reasonably resembles the temperature profile along the line (R-R) at different points. For example, at the center of the pipe within the fin the temperature is Tc, while the temperature at the edge of the fin is Tft. As shown in

this graph, the temperature in the gap between the fin and the interior wall increases and then decreases from the distal end of the fin to the interior wall. This temperature distribution occurs because the gap between the distal end of the fin and interior wall is too large. Accordingly, no thermal bridge is formed because heat is not transferred from the fin through the medium in the gap to the interior wall. Rather, heat is transferred from a location in the gap between the fin and the interior wall to both the fin and the interior wall.

8. In Exhibit C, I have provided a similar schematic view of the same vessel. However, the freezing is at a period in time when the frozen medium built up on the fin meets the frozen medium built up on the interior wall. To the best of my knowledge the temperature graph reasonably resembles the temperature distribution along the line (R-R) at different points. As shown in this graph, the temperature in the gap between the fin and the interior wall increases and then decreases from the distal end of the fin to the interior wall. This temperature distribution occurs because the gap between the distal end of the fin and interior wall is too large. Accordingly, no thermal bridge is formed because heat is not transferred from the fin through the medium in the gap to the interior wall. Rather, heat is transferred from a point in the gap between the fin and the interior wall to both the fin and the interior wall.

9. In Exhibit D, I have provided a similar schematic view of the same vessel. However, the freezing is at a period in time when the medium in the gap between the fin and the interior wall is completely frozen. To the best of my knowledge the temperature graph reasonably resembles the temperature distribution along the line (R-R) at different points. As shown in this graph, the temperature in the gap between the fin and the interior wall increases and then decreases from the distal end of the fin to the interior wall, even when the medium is frozen. This temperature distribution occurs because the gap between the distal end of the fin and interior wall is too large. Accordingly, no thermal bridge is formed, even after the medium in the gap is frozen, because heat is not transferred from the fin through the medium in the gap to the interior wall. Furthermore, even after

additional freezing may occur, including total freezing within the vessel, no thermal bridge is formed in the gap area. Rather, heat is transferred from a point in the gap between the fin and the interior wall to both the fin and the interior wall.

10. With respect to the above-referenced application, a thermal bridge will not form if the gap between the heat transfer members and the interior wall of the vessel is too large, even after the medium in the gap is frozen. If this gap is too large, heat would be transferred from a location within the gap to both the heat transfer member and the interior wall similar to the Genentech device, not from the heat transfer member to the interior wall as required by the formation of a thermal bridge.

11. I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in this Affidavit is true and correct.

January _23__, 2002 _____
Richard Wisniewski

EXHIBIT A

Proceedings of the International Congress

Advanced Technologies For Manufacturing Of Aseptic & Terminally Sterilized Pharmaceuticals & Biopharmaceuticals

Basel, Switzerland
17-19 February 1992
Convention Center Basel

Presented By The Parenteral Drug Association, Inc.
In Cooperation With The Association Pour Les Produits Parenteraux et Steriles (A3P) And The Parenteral Society

Advanced Technologies for Manufacturing of
Aseptic and Terminally Sterilized Pharmaceuticals
and Biopharmaceuticals

17-19 February 1992
Convention Center Basel
Basel, Switzerland

BIOPHARMACEUTICALS

CLOSURE TECHNOLOGY

FILLING

AUTOMATION

LARGE-SCALE FREEZING AND THAWING OF BIOPHARMACEUTICAL DRUG PRODUCT

Richard Wisniewski, *Process Development, Genentech, Inc.*
Vincent L. Wu, *Pharmaceutical Manufacturing, Genentech, Inc.*

Richard Wisniewski *is currently a Scientist with the NASA Ames Research Center, Life Sciences Group, in Mountain View, CA. He holds an M.Sc. in Mechanical Engineering from Warsaw Technical University. Wisniewski has a wide variety of experience in process development and equipment design for processes in the chemical, food and drug industry.*

Vincent L. Wu *is a Manufacturing Engineer at Genentech, Inc., in South San Francisco, CA where he is responsible for development and support of biopharmaceutical manufacturing aseptic processes. Wu holds a B.S. in Chemical Engineering from the University of Michigan.*

ABSTRACT

This study reports the successful implementation of mechanical-based refrigeration systems and vessels designed for the freezing and thawing of bulk protein solutions. Design principles for large- scale, freeze-thaw refrigeration equipment, freeze-thaw vessel, and controls are discussed. Freezing and thawing process validation methods and the effects on protein product are presented. The purified bulk product can be sterile filtered into the freeze-thaw vessel, frozen, and stored in a stable state until product is needed for filling. The frozen drug product may be shipped, thawed, pooled, filtered, and ultimately filled into vials. The stainless steel freeze-thaw tank design is compatible with current pharmaceutical manufacturing operations including product transfer, clean- in-place, and steam-in-place procedures. The authors believe that large-scale freezing is a viable and economical alternative for the intermediate storage and handling of sensitive bulk biopharmaceutical drug product.

Key Words

Convection
Cryoconcentration
Eutectic
Formulation
Freeze-thaw
Heat Transfer
Protein Stability
System Design

Introduction

Depending on the stability and storage period desired biological products are often stored at 2-8 °C, -20 °C, -70 °C or are lyophilized. The ability to freeze the formulated bulk protein product in a portable stainless steel vessel sized to the batch yield has many advantages. Since the yields of biotechnology products are relatively small and the difference in cost and time for filling and finishing small versus large production lots is minimal, the ability to store and pool offers an economy of scale advantage. Per unit cost quality control expense is also reduced. The ability to store bulk material for prolonged periods of time allows for campaigning of production facilities while maintaining the flow of product. The ability to store sensitive product in the frozen state allows transport of product that may not otherwise withstand liquid shipment. Product with short liquid shelf-life that is sensitive to protease degradation or deamidation may be frozen in bulk volumes prior to lyophilization.

The effect of long-term freezer storage, thawing and refreezing of select proteins in serum have been investigated by DiMagno, et al (1). Many of the hormones reported were stable at -20 °C and -70 °C for up to ten years. Schiewe and Rau reviewed processes and available equipment for deep freezing in biological and medical applications (2).

Upon the outset of the project there was no satisfactory method available to freeze and thaw large volumes of protein solutions under the conditions complying with the cGMPs. Freezing in small containers such as blood bags or vials is labor intensive requiring filling and capping equipment in addition to the freeze-thaw systems and agitation equipment for thawing. Product transfer, storage, recovery and handling in a portable stainless steel vessel were deemed superior to alternative methods.

Freezing

The freezing process involves solidification phenomenon with the solid-liquid interface moving and latent heat release at the interface. The latent

heat has to be removed by heat conduction through the solidified layer of material and through the heat exchange surfaces.

The movement of a solid-liquid interface may cause a phenomenon of redistribution of solutes. If the concentration of the solutes at the interface exceeds the diffusional effects for solute molecules, then cryoconcentration occurs. This phenomenon of solute redistribution has been analyzed by many researchers (3,4,5).

Korber and Scheiwe have provided experimental evidence confirming this phenomenon as well as an analysis of dendritic growth or branching ice crystal growth (6,7). Granger et. al., have developed computational methods to analyze the solute redistribution by moving solid-liquid interface and related effects (3).

For large volumes of freezing solutions, such as the system described here, solute redistribution effects may be of lesser significance due to natural convection effects and due to the relatively low velocity of the moving solid-liquid interface. It is predicted that natural convection plays a more significant role in larger volumes of liquid due to larger temperature gradients within the bulk. The low velocity of the liquid-solid interface in the large-scale system may allow greater solute diffusional effects reducing the effect of solute redistribution at the solid-liquid front.

If the growth of dendrites is comparable to the diffusional rate of dissolved molecules, for example proteins in this case, then the cryoconcentration phenomenon could be minimized and solutes may be entrapped between the progressing dendrites at relatively low concentrations. Smaller molecules, however, such as buffer salts in this case, may diffuse at a faster pace and be pushed in front of the dendrites with a gradually increasing concentration in the liquid phase and become excluded from the frozen mass of material. This phenomenon was examined in the designed freeze-thaw tank system and explains why samples taken at the unfrozen cavity significantly increased in ionic strength (indicating increased concentration of salts) and yet the concentration of protein at the unfrozen cavity did not differ greatly from the starting protein concentration.

There is evidence in the literature that proteins can be affected by changes occuring in the liquid phase during freezing, like increases in salt concentration and changes in pH (8,9,10,11). It was feared that during freezing, cryoconcentration effects may cause crystallization of buffer components leading to pH change which would effect protein stability or cause the protein to unfold or amino acid chains to be cleaved. Also, cryoconcentration effects combined with low temperature effects may cause a decrease in protein solubility and hence precipitation. In the system studied, the ability of the protein to maintain a certain percentage of single chain molecule and the efficacy of the drug was tested before and after repeated freeze-thaw cycles (see Figure 4).

Protein drug formulations may include a wide variety of compounds. Stabilizing agents or cryoprotective agents including for example sugars, glycols, glycerol, sodium glutamate, sodium acetate, potassium phosphate, serine and alanine may be considered during the formulation development (12,13,14). Consideration should be given to the final formulation to avoid low temperature freezing and to allow stability at warmer temperatures. For example, avoid using high concentrations of salts which may depress the freezing point, promote precipitation, or cause protein denaturation.

There is limited information available in the literature on the behavior of proteins at low temperatures (8,10,15,16,17,18,19) on formulations composition (9,20,21) and on specific cryoprotectant-type formulations (13,22,23,24), although those sources can be used rather as references only, and a need for an individual approach to each molecule of interest may be anticipated.

Protein stability and conformation can be affected by low temperature alone, for example without any significant changes occuring in solution like salt concentration or change in pH (8,16,17,18, 19,22, 24,25).

Thawing

The thawing process has quite different thermodynamic requirements when compared to freezing. During thawing, the liquid phase appears first at the heat transfer surface and it quickly separates the frozen product mass from the heating surface. Since the protein solution cannot be over-heated, the temperature of the heating surfaces should be maintained below a certain limit at which the product is stable, for example, about room temperature. At limited temperature gradients, natural convection in the liquid phase is limited even if the configuration of the heat transfer surfaces provides favorable conditions for natural convection. Research

done on natural convection during melting has shown that the influence of natural convection on acceleration of the melting rate increases with the height of the heat transfer surface (26,27). The top of a liquid cavity becomes much wider than the bottom part due to warm currents which rise along the heated surface and descend along the frozen mass boundary.

Our interest turned to methods to increase the movement within the liquid phase. An agitator in the tank was considered impractical, since the agitator would be enclosed in the frozen mass for too long to be effective. Recirculation of the thawed liquid from the bottom of the tank to the top of the frozen mass at a slow rate was found to be suitable and aseptic and allowed recirculation to occur relatively early in the thawing cycle.

To determine the point during the thawing cycle when recirculation should begin, there must be adequate liquid phase at the tank bottom and sufficient melting at the tank walls so that the liquid can be pumped from the tank bottom, to the top of the frozen mass, around the ice mass, and return to the bottom. The use of sterilized silicone tubing and a peristaltic pump was found to be suitable and aseptic for product recirculation during thawing. A product recirculation rate at two times the average melting rate was effective for thawing and for producing homogeneous bulk product by the end of the thawing process. The recirculation tubing was also useful for sampling and for transferring the product to another vessel at the end of the thawing process. See Figure 1.

Another option for providing agitation during thawing is to shake or move the entire tank on a mechanical shaker platform. In this case, frozen masses float in the liquid phase and causes stirring of the liquid phase by relative solid-liquid movement. This method is quite simple and aseptic, however it requires heavy equipment and vibrators and is more expensive to scale up.

Freeze-thaw Vessel Design

Since the product of interest was a parenteral drug, containment was a critical issue, and since the product could be subjected to a slow freezing rate, a jacketed tank system with recirculating heat transfer medium was chosen over freezing with liquid nitrogen. There are many problems with immersion of a large container in liquid nitrogen including thermal stress to the container, efficient removal of bubbling cold gas, and in general complicated handling of the container would be involved.

The problem with freezing and thawing in a jacketed tank is that heat transfer decreases significantly after reaching a certain thickness of frozen material, due to poor heat conduction through the frozen mass. Two conditions which improve heat transfer include the use of a large temperature difference between the cooling medium and the liquid being frozen, and the use of extended heat transfer surfaces.

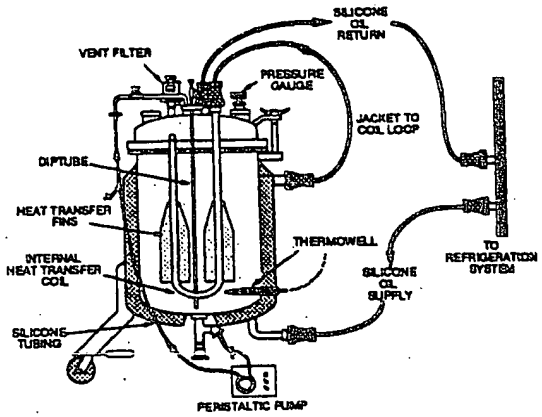


Figure 1. Freeze-thaw Vessel: Thawing Configuration

The freeze-thaw tank design could be in the form of a cylindrical, jacketed vessel of small diameter and large height. However, such a design is not economical and there is a possibility of developing significant mechanical stress in the side walls from expansion during freezing. To increase the product volume and to use a tank of more conventional proportions a heat transfer coil was added to provide additional heat transfer surface. The coil was in the form of a 3.35 meter (11 foot), one inch Schedule 40 (316L) seamless pipe with three 180 degree bends. Heat transfer fins were welded to the external surface of the pipe (28,29). The fin design was analyzed using a computer model. The fin's length, thickness and shape were designed to maintain efficient heat transfer during freezing and thawing. The fin performance characteristics are based on it having a higher thermal conductivity than the frozen material. One important requirement is that the fins must be of sufficient thickness to allow adequate heat transfer by conduction towards the wall of the pipe. The heat transfer surface configuration was designed to minimize internal mechanical stress caused by expansion of the freezing mass and to induce freezing from the bottom of the vessel upwards by providing more heat transfer surface at the tank bottom. Natural convection and surface freezing effects were taken into consideration in the fin design to prevent rapid

Several design considerations may be implemented to allow the refrigeration system to operate at the lowest possible temperatures. The backpressure valve after the evaporator can be oversized and kept almost open or it could be completely removed from the circuit if the lines are properly sized. The suction accumulator performance becomes critical especially at the end of the freezing cycle and it should be heated by electrical coils or hot gas refrigerant coils.

The condenser should be cooled with refrigerated water or glycol to keep the temperature of the condensed refrigerant as low as possible. To aid in the fine tuning of the refrigeration system, thermocouples may be attached to the refrigerant piping at critical points in the system to monitor the refrigeration system performance. These temperture readings can become a part of an overall system control and diagnostic scheme.

Another factor to consider is the properties of the heat transfer medium for freezing and thawing. It should be non-toxic, have a very low freezing point and low viscosity at low temperatures. Its thermal properties should assure sufficient heat transfer coefficients in the tank jacket and in the evaporator of the refrigeration system. During the thawing process the heat transfer medium is heated and therefore it should not evaporate or degrade during heating. It should also be non-flammable, non-corrosive and compatible with stainless steel (chloride-free).

Our attention focused on silicone fluids of low viscosity. For example, Dow 200 Fluid with 5 centistoke viscosity can achieve approximately minus 60 °C, while its boiling point is still high enough for heating during thawing. If a lower viscosity fluid is considered, such as 1 centistoke Dow 200 Fluid, then its boiling point temperature may not be well suited for the heating duty during thawing. Also low viscosity fluids have relatively low flashpoint temperatures and may pose a flammability danger in open systems.

The recommended upper operating temperature limits for the 1 and 5 centistoke Dow 200 Fluids are 32 °C and 65 °C respectively. Since the 5 centistoke fluid had a flashpoint of 133 °C it was chosen as a heat transfer medium for applications involving thawing at moderate temperatures. The viscosity of the 5 centistoke fluid at minus 60 °C is approximately 75 centistokes.

The pump used for recirculating the heat transfer medium should be designed so that the addition of heat is minimized. This can be accomplished by selecting a pump design configuration that allows effective dissipation of heat from the motor, and by implementing a pump with high pumping efficiency, working at its optimum point on the pump curve. The optimum working point on the pump curve should be determined at the higher fluid viscosity at the lower end of the working temperature range. A seal-less, leakproof canned motor pump can be suitable.

The design of the refrigerant evaporator should ensure turbulent, high velocity flow of heat transfer medium around the bundle of evaporator tubes. Moisture in the heat tranfer medium can create operational problems including ice build-up on the evaporator tubes. A moisture trap should be installed in the system such as a dessicant type filter drier cores. A multiple moisture trap design is recommended to allow an undisturbed system performance in the event that traps need to be changed during the operation.

The heater used to heat the heat transfer medium during the thawing process can be on a separate branch of the piping or it can be installed in the heat transfer fluid reservoir. An electric heating element, controlled by a proportional controller is suitable. To maintain temperature control over the heat transfer fluid during thawing a separate cooler is needed to prevent overheating of the heat transfer fluid. This cooler should be situated downstream of the heater. The cooler can be a heat exchanger with refrigerated glycol as a cooling medium, or a small mechanical refrigeration unit.

Figure 2 shows a freeze-thaw system design capable of freezing and thawing multiple tanks. The R-502 refrigeration system is utilized for freezing and the R-12 refrigeration system used in conjunction with the heater in the reservoir is utilized for thawing. Compressed air is used to recover the heat exchange media from the tank jacket and heat transfer coil at the end of the freeze and thaw processes.

General System Performance

During the freezing process, the thermal load on the cooling system varies due to an increase in the thickness of the layer of frozen material at the heat transfer surfaces. At the beginning, the heat load is high due to cooling of the tank and the liquid product and due to a release of latent heat from the first, thin layer of rapidly freezing product on the heat transfer surfaces.

freezing of the upper levels of the liquid and to avoid liquid phase entrapment under frozen surfaces.

The approach was to design the freezing vessel in such a way to minimize cryoconcentration effects and provide a uniform freezing rate with the protein molecules being occluded by the moving freezing front. The heat transfer fins were configured to divide the tank volume into compartments to decrease the freezing and thawing time and to reduce cryoconcentration effects. Compartmentation of the tank is especially effective for maintaining liquid in a static state to minimize cryoconcentration. A full external dimpled-type jacket which extended to the tank bottom was also provided and the vessel was well insulated with compressed chloride-free insulation. To improve radiant heat transfer effects and to aid cleaning, the internal surfaces of the vessel including the internal heat exchanger surfaces were polished to 320 grit (10 ra) and electropolished to provide a mirror finish.

The vessel was designed to be compatible with current pharmaceutical manufacturing operations including sterilization-in-place and clean-in-place. The vessel was constructed according to ASME code to withstand steam sterilization and was rated for full vacuum. Multiple spray devices inserted into the vessel were designed for the vessel to provide thorough cleaning of the internal heat exchange surfaces.

Refrigeration System

The refrigeration system was developed using engineering principles similar to those of a freeze-drier. It was known from laboratory experiments, that the product was able to be frozen to -20 °C and thawed at 2-8 °C in vials without deleterious effects.

Mechanical refrigeration systems used to cool the heat transfer media have limits regarding the lowest achievable temperatures, depending on the refrigerant used and the design principle. For instance, refrigerant R-502 allows temperatures in the evaporator to reach a level as low as minus 50-53 °C and the refrigerant R13B1 achieves about minus 65-67 °C with a two-stage compressor (30). Figure 3 shows the temperature of the coolant over time without a load. The versatile system which may be utilized for freezing and thawing of protein solutions should have the capability of providing well controlled, varying cooling and warming rates. The cooling rate can be controlled, for example, by oversizing the compressor and utilizing a bypass loop to the heat exchanger to control the amount of recycling of the recirculating heat exchange media. If very low temperature applications are required a cascade refrigeration design may be considered, or the heat transfer fluid may be cooled using liquefied gases.

Since the load on the refrigeration system varies significantly and there is a prolonged period of operation at a very low load at the end of the freezing cycle, selection of the evaporator expansion valve is of particular importance in avoiding evaporator flooding at low loads.

A synthetic lubricating oil for the compressor which performs well for prolonged work and at low temperature should be selected over hydrocarbon oils which break down and become viscous at low temperatures.

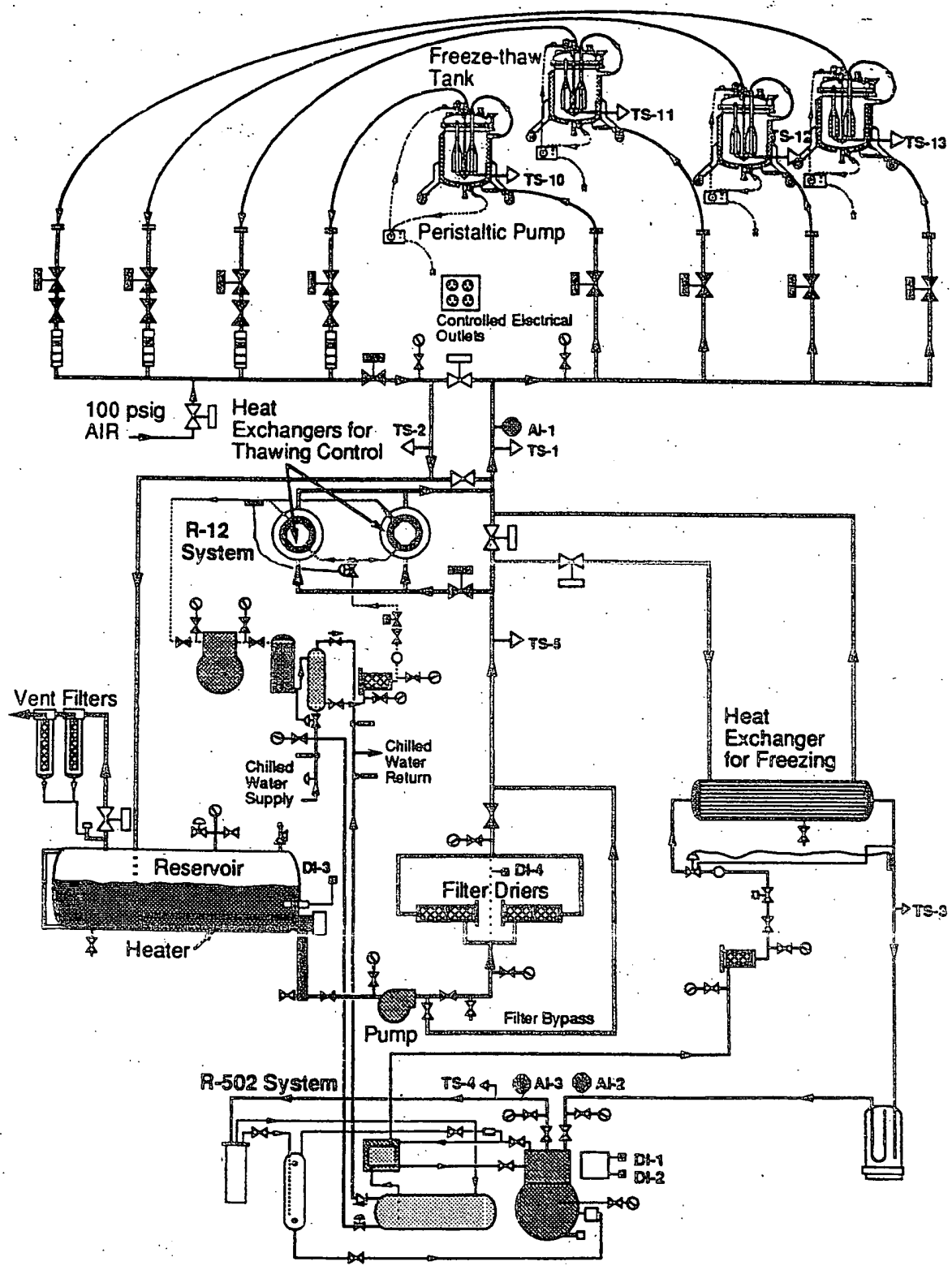


Figure 2. Refrigeration System and Freeze-thaw vessels in multiple thawing configuration

As soon as the layer of frozen material appears on the heat transfer surface, the heat flux begins to decline due to heat conduction through the frozen material and an increased resistance to heat transfer. Heat conduction through frozen material quickly becomes the controlling factor over freezing rate and overall heat transfer. Computer models have been developed to predict the heat flux decline and the movement of a freezing front. Figure 3 shows the freeze-thaw temperature profile for freezing and thawing during one of the test runs.

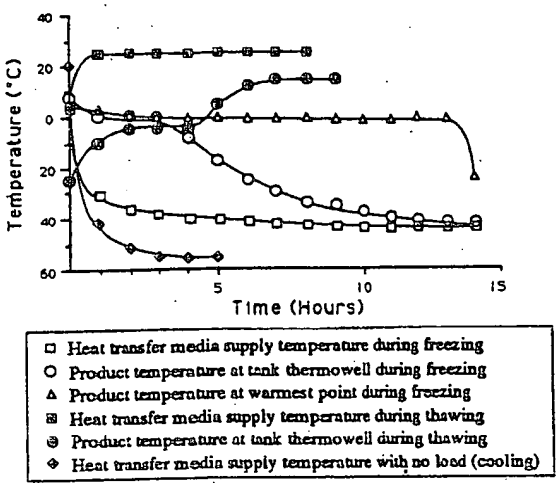


Figure 3. Freeze-thaw Temperature Profiles

Validation

Validation of the freezing endpoint can be achieved by determining where the warmest point in the vessel is located or where the final liquid cavity exists. In our case, this location has been determined to be the top center surface of the liquid. During freezing this location was the last point to achieve the desired temperature. Ideally, a temperature sensor for process control should be located at the warmest point in the vessel. However, to accomodate freezing of a variety of liquid volumes, the temperature sensor would need to be relocated for each volume or several temperature sensors located at strategic points would be required. For example, a thermocouple suspended on a float could place the thermocouple near the liquid surface. However, this configuration does not lend itself to aseptic design because of suspended thermocouple wires which are a hindrance to cleaning and sterilization.

The use of a thermowell located at the side of the vessel or at the bottom of the vessel was found to be an acceptable design solution. The thermowell should be located at a low level inside the tank since its location determines the minimum liquid volume allowable to be frozen or thawed with the tip of the thermowell in the solution. If temperature control is performed using a temperature sensor in a location other than the warmest point in the tank, a corresponding temperature setpoint for the thermowell must be determined based on the achievement of the desired temperature (for example -20 °C) at the warmest point in the tank. The maximum liquid volume should be used to determine the thermowell setpoint temperature. It has been proven that less than maximum volumes are thoroughly frozen upon achievement of the determined thermowell setpoint temperature.

While the freezing process continues until the temperature reaches the validated temperature setpoint, the thawing process is best terminated by a validated time setpoint. Since loose floating masses of ice exist toward the end of the thawing cycle, it is difficult to determine the thawing endpoint solely by monitoring temperature. During validation one must visually verify the end of the thawing process by verifying the absence of frozen mass. The tank must have sightglasses or ports to inspect the bulk solution for validation purposes. Also, samples of the thawed bulk solution should be taken from the top, middle and bottom of the vessel and assayed for protein concentration to verify that the thawed mass is homogeneous.

A thawing scheme has been developed based on time to thaw the maximum volume. Smaller volumes thaw within the established time to thaw the maximum volume. The temperature of the bulk solution can be controlled by stopping the supply of the warming media to the tank jacket and internal coil when a certain product temperature measured at the tank thermowell is met and restoring flow of the heating medium when the temperature of the product decreases below a certain level. During this cycling process, the liquid product continues to be recirculated causing the liquid to cool and the frozen mass to recede.

Determination of the thawing media temperature should be based on stability data of the product since a film layer of product is subject to the temperature of the warming media at the heat transfer surfaces. For the purpose of thawing at the maximum possible rate, the temperature of the media used for thawing should be the maximum temperature that the product will tolerate for a reasonable period of time. For

protein products frequently this may not be more than room temperature (about 25 °C).

	Sample Position (in tank)	pH 7.1 ± 0.1	Protein 1.5 ± 0.1 mg/ml	Activity ≥1.9 U/mg	Single Chain > 80 %
Freeze Cycle 1	Top	7.1	1.490	1.990	94.70
	Middle	7.1	1.480	1.910	94.60
	Bottom	7.1	1.440	1.930	94.10
Freeze Cycle 2	Top	7.1	1.430	2.030	94.50
	Middle	7.1	1.440	2.030	94.70
	Bottom	7.1	1.420	2.030	94.40
Freeze Cycle 3	Top	7.1	1.450	2.010	94.40
	Middle	7.2	1.430	2.020	94.50
	Bottom	7.1	1.420	2.020	94.60

Figure 4. Effect of repeated freeze-thaw cycles on a protein product (example results)

Figure 4 shows the effects of repeated freezing and thawing of a protein product in a 150 liter stainless steel portable tank. The product was frozen to -20 °C and subsequently thawed with 25 °C warming media for 9 hours. The data illustrates the ability to freeze-thaw multiple times without deleterious effects. The top row indicates the desired product specifications. Product has been stored at -20 °C for over two years without degradation.

Conclusion

Before proceeding to freeze and thaw large volumes of protein solutions the stability of proteins at various temperatures should be known. The eutectic temperature should be known as well as the stability at room temperature. The behavior of the formulating buffers during cooling, freezing, and concentration should be investigated. If bulk freezing is considered part of the process from the outset, the formulation buffer should be developed to provide eutectic freezing and protein stability at warmer temperatures, for example, at -20 °C rather than at -70°C.

The design of the freeze-thaw container should include extended heat transfer surfaces and provide division of the liquid volume into compartments to prevent cryoconcentration effects. In the case of aqueous solutions, precautions should be taken to minimize structural stress in the freezing containers caused by product expansion. Heat exchange surfaces should be designed to cause freezing to proceed from the bottom to the top of the container and to avoid formation of entrapped liquid cavities which may damage the vessel upon freezing.

Forced convection by recirculation of product during thawing from the bottom of the vessel to the top and over the ice mass is an effective method for accelerating the thawing rate and maintaining homogeneity of the bulk protein solution.

If the protein product is a human therapeutic, then the container design must meet cGMP requirements. The stainless steel tank design should be configured for clean-in-place and sterilization-in-place procedures and be capable of holding sterile product.

Scaling up of the process of freezing and thawing from vials to the large scale should be approached with caution due to uncertainty of cryoconcentration effects. If freezing and thawing of the protein product can be successfully achieved in vials it is possible that freeze-thaw can be accomplished on the large-scale.

Full testing of the product for stability after freezing and thawing for multiple cycles should be performed to examine the detrimental effects of freezing and thawing including assays on the protein structure, protein concentration, protein activity, pH, color and appearance, and specific binding assays.

Generally the warmer the allowable storage temperature the more economical and practical is the application for large-scale freezing and thawing. For freezing to temperatures less than -50 °C, mechanical refrigeration methods may not be practical. Also, freezer storage and frozen bulk handling becomes a problem with larger bulk size and lower storage temperatures.

The mechanical-based refrigeration system is a feasible design for the freezing and thawing of bulk protein solutions. Careful attention should be paid to its overall design and component selection.

Acknowledgements

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EXHIBIT B

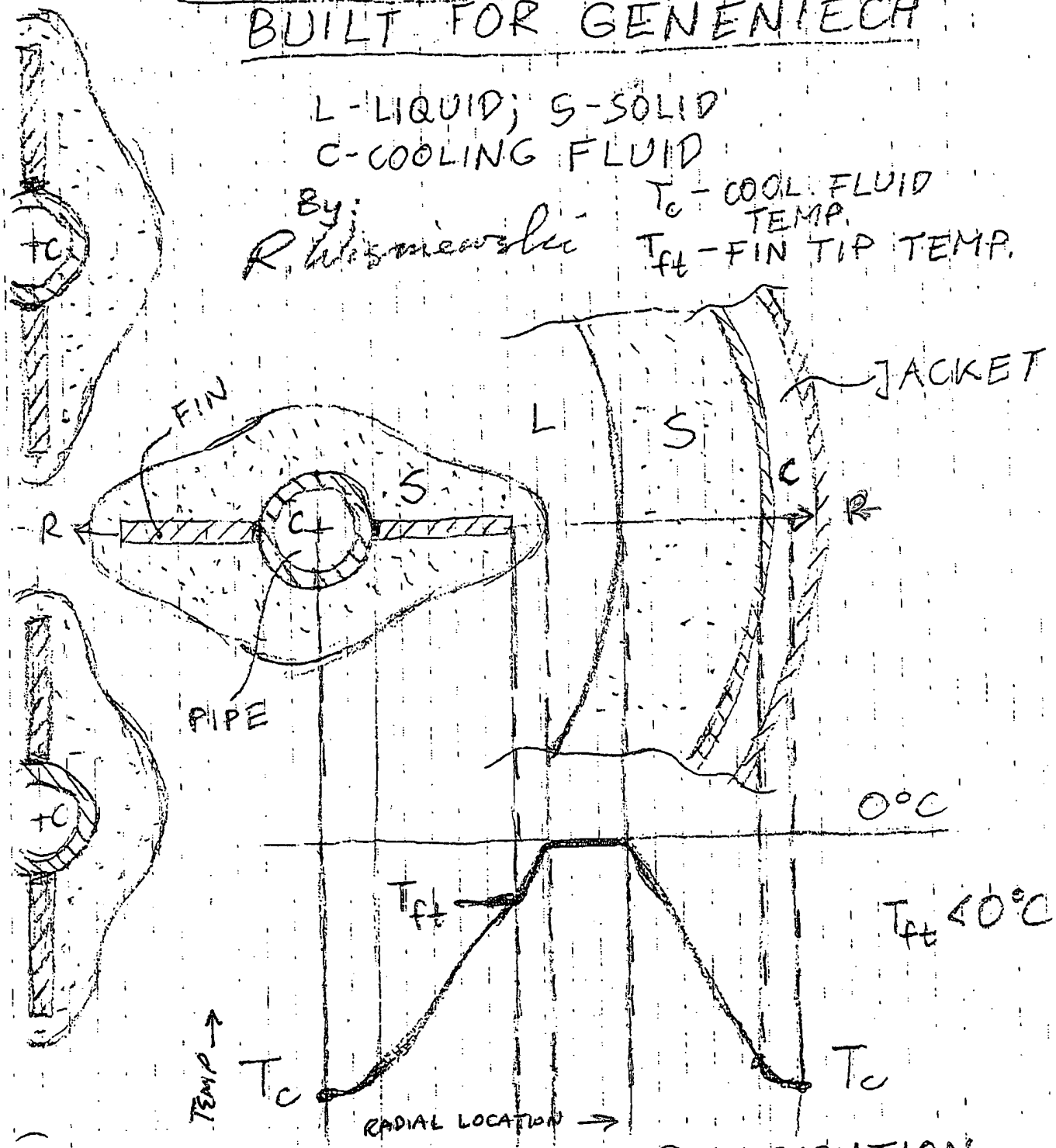
TO: NICK MESITI
JAN. 05, 2002 (1.)

FREEZING IN 103 L VESSEL BUILT FOR GENENTECH

L - LIQUID; S - SOLID
C - COOLING FLUID

By: R. Weismeerblee

T_c - COOL. FLUID TEMP.
T_{ft} - FIN TIP TEMP.



TEMPERATURE DISTRIBUTION

EXHIBIT C

JAN. 05. 2002 (2)

103L GENENTECH VESSEL

T_{ft} - FIN TIP TEMP.

[FRONTS MEET]

By R. Wiśniewski

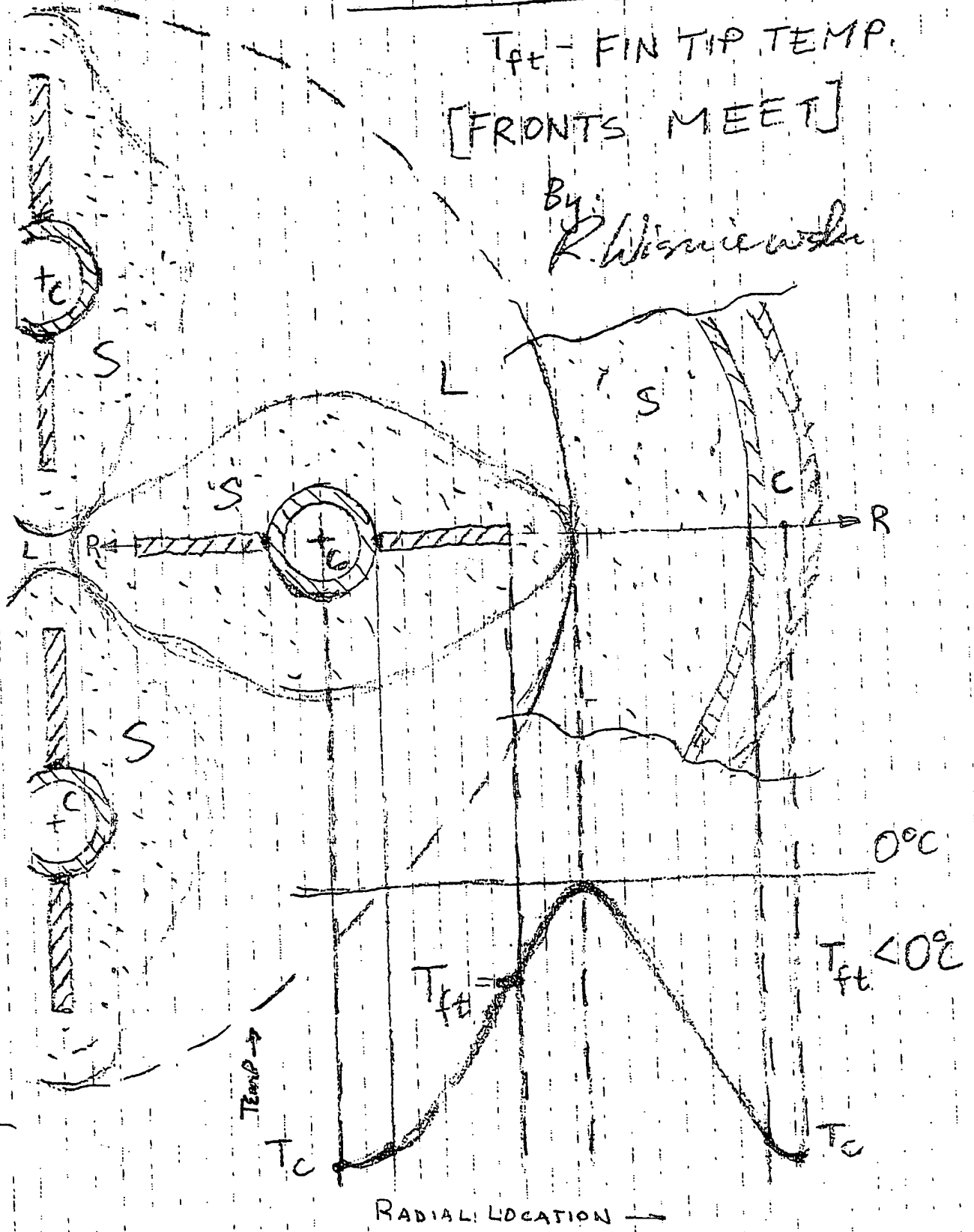


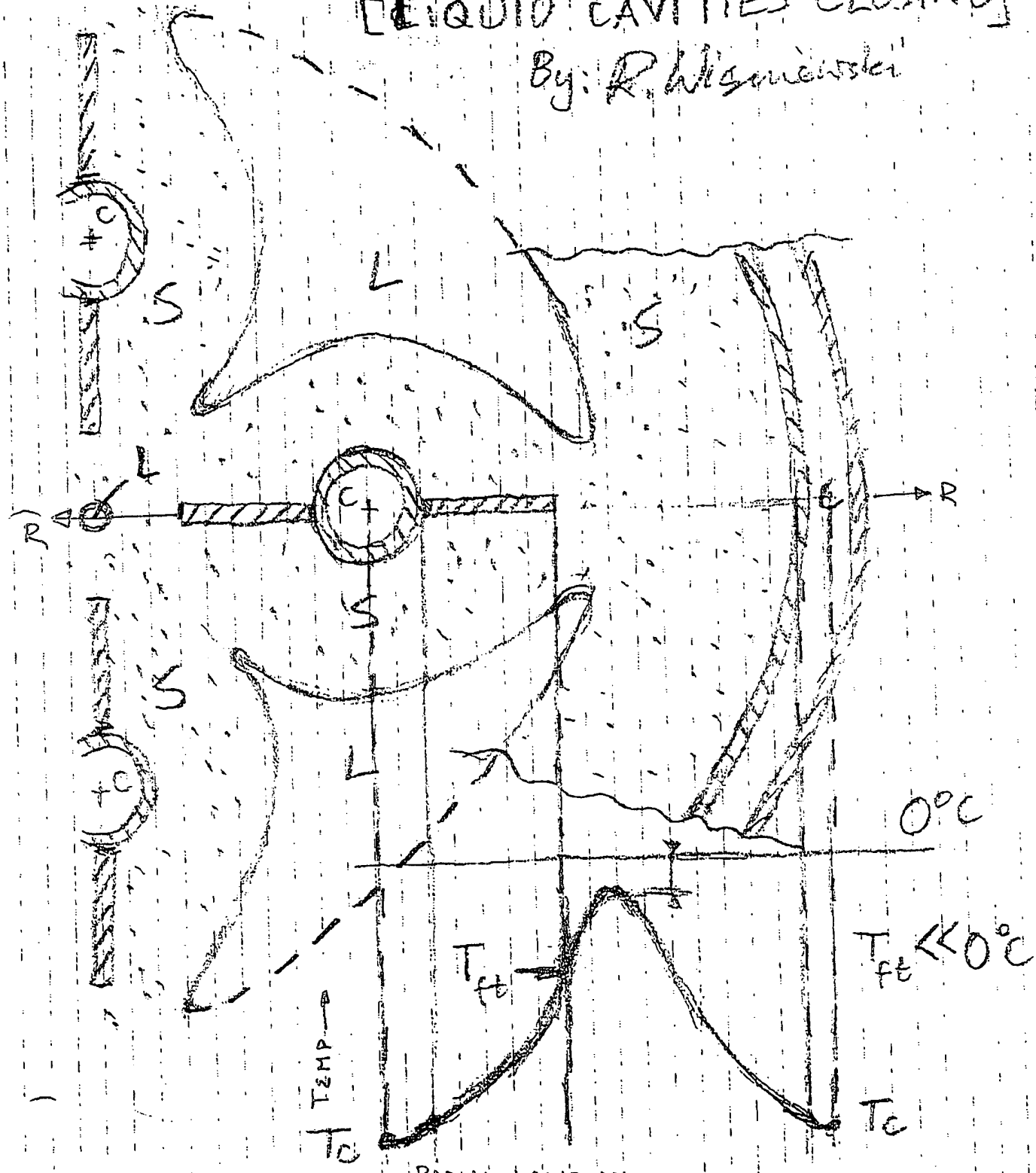
EXHIBIT D

JAN. 5, 2002 (3.)

103L GENENTECH VESSEL

[LIQUID CAVITIES CLOSING]

By: R. Wisniewski



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	WISNIEWSKI et al.	Group Art Unit:	3743
Serial No.	:	08/895,936	Examiner :	John Ford
Filed	:	July 17, 1997		
For	:	FREEZING AND THAWING VESSEL WITH THERMAL BRIDGE		

Commissioner for Patents
Washington, D.C. 20231

SECOND DECLARATION OF RICHARD WISNIEWSKI

1. I am one of the inventors of the above-referenced United States patent application. I am also a named inventor of six U.S. Patents relating to cryopreservation of biopharmaceuticals and numerous pending patent applications. I make the statements herein to the best of my own personal knowledge.

2. I received degrees in Mechanical Engineering and Chemical Engineering from Warsaw Technical University in Warsaw, Poland in 1971. I have over 26 years of experience in applied research, process and product development, process control, equipment and device design, industrial facility design and project and team management in the biopharmaceutical field.

3. I am a co-founder and currently the Chief Technology Officer of Integrated Biosystems, Inc.

4. Prior to my current position, I have held senior engineering and management positions with Wyeth-Ayerst, Genentech, Inc., Bepex Corporation and Ares Serono. While at Genentech, Inc., I was a Principal Process Engineer responsible for pioneering work in

the design of equipment and processes for biopharmaceutical manufacturing, including systems for cryopreservation, chromatography, filtration and bioreactors and aseptic processing used in large scale production. I do not currently work for Genentech and have not worked for Genentech for over a decade, since January of 1991.

5. While I was working for Genentech, Inc., I co-published, with Vincent L. Wu, an article entitled "Large-Scale Freezing and Thawing of Biopharmaceutical Drug Product" for the Advanced Technologies For Manufacturing Of Aseptic & Terminally Sterilized Pharmaceuticals & Biopharmaceuticals convention during the Proceedings of the International Congress in 1992 ("the 1992 article"). This 1992 article is similar to the 1996 article previously disclosed to the Patent Office during the prosecution of the above-reference application.

6. I have read and am familiar with the most recent Office action mailed January 29, 2003 in connection with the above-identified application.

7. In the specification of the above-identified application, the first two paragraphs under the heading "2. Description of the Prior Art" refers to the Genentech device disclosed in the 1992 Wisniewski and Wu publication. Other than the 1992 Wisniewski and Wu publication, I do not have any further documents relating to the Genentech device, including any specifications on the distance between the fin tip and the interior vessel wall.

8. However, to the best of my knowledge, Exhibits B, C and D of my first declaration reasonably resemble the temperature distribution of the 1992 Genentech container and the drawing of the Genentech device in the 1992 article accurately represent a scaled down version of the device. Thus, the distance depicted in the 1992 article reasonably represents the relationship between the distance between the fins and the interior wall. Although I cannot remember the exact distance between the fin tip and the interior wall of the Genentech device, I know that this distance was greater than 4 inches. When I

designed the Genentech device, the distance between the fin tip and the interior vessel wall was not an important parameter. The fins of the Genentech vessel were small and thin, as shown in the 1992 Wisniewski and Wu publication, and designed only to aid the freezing around the loop pipe in order to increase the relatively small surface area of the pipe (e.g. adding more cold surface area). No thermal bridge was formed by the biopharmaceutical material between the fin tip and the interior wall of the Genentech device.

9. In the specification of the above-identified application, the third paragraph under the heading "2. Description of the Prior Art" refers to a container having ribs welded to the core and the interior wall of the vessel. Since the ribs were connected to both the internal core and the interior wall of the vessel, no thermal bridge can be formed by the medium between a fin tip and the interior wall of the vessel because there is no gap between the ribs and the interior wall of the vessel. Heat transfer occurs only through the external wall of the vessel. Although not relevant to the particular freezing of biopharmaceutical materials, an example of such a vessel is shown in U.S. Patent Nos. 2,441,376 to Stiening and 2,129,572 to Finnegan. To the best of my knowledge, such vessels were used in heat storage devices for, e.g., paraffin and comestibles.

10. Some time ago, I attended an Examiner's interview at the U.S. Patent and Trademark Office with David Abraham, Esq. from the law firm Wilson Sonsini Goodrich & Rosati. During that interview, I recall discussion of the Basel Pharmaceutical Meeting/Conference presentation document (Proceedings of the International Congress), which contained a copy of the 1992 Wisniewski and Wu publication. This presentation document was attached to my first declaration as Exhibit A. To the best of my knowledge, no actual device or other documents were discussed or presented at the meeting because no such device or documents were in our possession.

11. I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in this Affidavit is true and correct.

February 26, 2003

Richard Wisniewski